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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,726	11/28/2000	Gyula Hadlaczky	119354-00002 / 402E	7776

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/724,726	HADLACZKY ET AL.	
	Examiner	Art Unit	
	BRENT PAGE	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-52,73-79,81,84,87-95,97-99,101,104,108,111,114,115,117 and 119-121* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 50-52,73-79,81,84,87-95,97-99,101,104,108,111,114,115,117 and 119-121.

DETAILED ACTION

The Reply filed by Applicants on 01/31/2008 is acknowledged. The supplemental response filed on 02/06/2008 is also acknowledged and hereby considered. The signed declaration referred to as DECLARATION 7 is acknowledged and fully considered below.

Response to Preliminary Arguments

Applicants urge that the Examiner's rejections and responses to Applicant's arguments appear to be premised on the basis that the Examiner does not believe that SATACs can be generated in plants using methods exactly as described in the application and that the Examiner seems to question the validity of statements made in the DECLARATIONS.

The rejections of record and the responses to Applicant's arguments are based on the legal standard for patentability of the instant claims. All such statements are based on whether or not there is guidance in the original specification for practicing the invention as claimed, or sufficient written description to determine that Applicants had possession at the time of filing. While Applicants believe that the Examiner disagrees with the veracity of the statements, the Examiner notes that the Examiner has gone on record stating that the Examiner is not, in fact questioning the veracity of the statements submitted in the DECLARATIONS.

With respect to the other preliminary urgings it is believed that these topics are addressed specifically in the following office action.

Claim Rejections - 35 USC § 112

Enablement

Claims 50-52, 73-79, 81, 84, 87-95, 97-99, 101, 104, 108, 111, 114-115, 117 and 119-121 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was s not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims remain rejected for the reasons of record in the office actions filed 01/17/2003, 10/22/2003, 08/12/2004, 05/09/2005, 03/30/2006, and 07/31/2007 as well as the reasons presented below.

Applicant's arguments filed 01/31/2008 have been fully considered but they are not persuasive.

Applicants urge on page 9 of the response that "the Office Action cites numerous (post filing date) references that are not relevant to satellite artificial chromosomes", and on page 10 of the response that the application teaches introduction of a SATAC including a plant SATAC, into a cell, including plant cells or protoplasts, and the generation of transgenic plant therefrom.

This is not persuasive because the art cited in previous office actions mailed out 01/17/2003, 10/22/2003, 08/12/2004, 05/09/2005, 03/30/2006, and 07/31/2007, all deal with the structure and composition of mammalian and plant chromosomes. Applicant has defined a SATAC to include certain essential elements, including a centromere, and

an origin. Given that the cited art establishes the state of the art of each of those elements post filing date, it demonstrates that particular features of the claimed invention were unknown and unpredictable. It is unclear what the relevance is of the apparent issue of "post-filing date" is in regard to the references in the rejections of the instant application. What is unknown and unpredictable post-filing date is going to recognized as unknown and unpredictable also at the time of filing. Furthermore, Applicants as discussed in prior office action do not teach the introduction of a plant SATAC into plant cells or protoplasts or the generation of transgenic plants therefrom. The instant application only teaches that of mammalian SATACs introduced into a cell. As mentioned in previous office actions, there is no mention in the application of a plant SATAC, no sequences associated with a plant SATAC, no methods for performing the claimed methods on plant cells that take into account the plant cell wall, an issue that was still unresolved at the time of filing, nor the methods on plant protoplasts.

Applicants further urge that none of the cited references offers any evidence that the methods of the instant application do not result in the production of plant artificial chromosomes and that one does not require knowledge of plant chromosomal structure or sequences or centromeres or other methods.

This is not persuasive because the references go into detail on the differences between plants and animals at the chromosomal level and establish that there would be no expectation of success in applying the taught methods for mammalian SATACs to plant cells to generate plant SATACs. One of skill in the art would not have expected the same result following the exact same steps as provided in the application for

mammalian cells. However, in addition to this lack of expectation, there are numerous differences in the methods exemplified for mammalian cells versus those disclosed in DECLARATION 5 and DECLARATION 7. As to one not requiring the knowledge of plant centromeres, this appears to go against Applicants own teachings. For instance, in the instant application, on page 88 Applicants disclose "To determine whether mouse centromeric sequences had participated in the amplification process forming the 'sausage' chromosome and whether or not the amplicons carry inactive centromeres, in situ hybridization was carried out with mouse minor satellite DNA. Mouse minor satellite is located specifically near the centromeres of all mouse chromosomes". The DECLARATIONS of record, particularly DECLARATION 5 and DECLARATION 7 do not disclose using plant centromeric sequences for identification of the plant centromere, nor do they disclose using sequences known to be near the centromeres of each chromosome. As to one not requiring the knowledge of plant chromosomal structures, this too, appears to go against Applicants own teachings. The specification also teaches that mouse chromosome 7 was identified by characteristic G-banding on page 30 of the instant specification. There is no identification of peculiar chromosomal features in the DECLARATIONS that would lead one to know that any part of any particular chromosome is, in fact incorporated in the SATAC as taught in the specification. Furthermore there were no resources available at the time of invention that would be able to similarly identify that the same process was taking place in the plant cell or plant protoplast. The specification indicates that such identification steps are critical to the invention and critical to the isolation of the SATAC as well as the

propagations of the SATAC. Without the ability to properly identify the functioning embodiments, one of skill in the art would not be able to practice the invention as claimed and as outlined in the specification. As to one not requiring any additional methods, this appears to go against the state of the art and the teachings by Applicants of the essential destabilization step. Additionally, the specification describes in great detail the necessity of destabilization with BrdU, and mentions on page 115 that the "results indicate that (i) the incorporation of BrdU is a rapid process.." which is contrary to the state of the art in plants where there are known difficulties in BrdU incorporation. Yet none of the declarations mention BrdU incorporation, and since there is no guidance in the specification it would be undue experimentation to merely apply the exact same methods to plant cells or protoplasts as broadly claimed and urged. The specification also goes into great detail on pages 126-128 regarding the differences of particular cell lines and how that would affect the methods used. However, the specification gives no guidance as to what changes would be made with the use of plant cells. While discussing the differences of chromosome number and chromosome size, there is no discussion of content and no discussion of the very different chromosome size and DNA content of plant cells. These differences are furthermore not discussed or addressed in the declarations of record. The assertion by Applicants that no knowledge of these plant specific structures and sequences is required is in contrast to the detailed teachings that enable Applicants for the generation of mammalian SATACs.

Applicants also urge that the absence of Applicant's claimed subject matter in the literature does not *a priori* support an enablement rejection, but rather it demonstrates its novelty (see page 11 of response).

This is not persuasive because the state of the art indicates there is nothing predictable in regard to the generation of artificial chromosomes in plants. Applicant is required to fully disclose guidance that would enable one of skill in the art to practice the invention. The mere assertion that aspects of the methods are standard in the art are not persuasive because as acknowledged by Applicant, there is no "standard" in the art as it regards generation of plant artificial chromosomes in plant cells or protoplasts at the time of invention. One of skill in the art would not assume, nor expect that routine materials and methods used on mammalian cells would automatically work on plant protoplasts, and indeed, differences are admitted by Applicant particularly as it regards identification steps, and cytological methods and materials, even though these differences are not described nor discussed in the specification.

Applicants further urge that enablement rejections may only be made where individuals of skill in the art state that a particular invention is not possible, and that none of the cited references make such a statement (see page 11 of response).

This is not persuasive because it is not necessary to provide evidence that something is not possible in order to support an enablement rejection. In fact, In Re Wright verified that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'". Where

a single example was given, the court affirmed that the Applicant was not enabled for the unpredictable embodiments where there was no expectation of success.

Applicant further urges that the declarations, particularly 5, 6 and 7 unequivocally establish that the methods may be applied to plant cells for the generation of plant SATACs (see page 11 paragraph 2 of the response).

This is not persuasive as discussed above, but will be separately addressed here for clarity. The declarations of record do not establish that plant SATACs were generated using the techniques described in the specification, and in fact, there are notable differences that, as they stand, would not enable one of skill in the art to practice the methods as outlined in the specification to generate SATACs in plants.

One major difference between the detailed specification as it regards mammalian SATAC generation and the declarations are the methods used to identify the various chromosomes and chromosome structures. The application and specification do not rely on primary constrictions to identify centromeres, but instead, disclose and use known centromeric sequences for the identification of sausage chromosomes as well as other SATACs. Furthermore, the specification uses banding patterns specific to particular chromosomes to identify which chromosome is incorporated into the SATACs. The specification does not outline any different method for chromosome identification for plants, does not address the necessary differences in plants, and does not disclose the structures and features that would be necessary for such identification. The declarations rely on the use of 18s rDNA probes and the probe for the selective marker to identify the same chromosomal structures. The problem with this method is that

neither of these probes identify or would allow one of skill in the art to recognize that any part of the plants endogenous centromere has been incorporated into the structure as shown in great detail in the specification for mammalian chromosomes.

The specification on page 17, discloses that the essential components of a SATAC are "at least the centromere and the origins of replication". Applicants appeared to fully recognize the necessity of providing the evidence for the presence of the centromere for mammalian SATACs as the specification details the identification with centromere specific probes, and also related the importance of cloning centromeric sequences for the construction of artificial chromosomes (see page 88 3rd paragraph and pages 44-45). Furthermore, the specification provides definitive evidence of an artificial chromosome with a fully functioning centromere on page 82 of the specification where it is fully recognized that long term culturing in non-selective conditions shows that the chromosome is stably maintained. In DECLARATION 5, Fabijanski discloses the methods of observing plant chromosomes and *in situ* hybridization. Fabijanski reports materials and methods not present in the specification, in particular the chromosome spreads for visualization. Furthermore, DECLARATION 5 provides no evidence of amplification or incorporation of a functional centromere in the resultant chromosomes other than the asserted primary constriction. As mentioned above, the specification provides evidence of the presence of centromeric DNA in the mammalian artificial chromosomes. And, as stated above and in the previous office actions, and as described in the specification, a functional centromere is REQUIRED for the generation of a SATAC. In order for Applicants to be enabled for the generation of plant SATACs

evidence must be present in the SPECIFICATION that functional embodiments can be obtained by the outlined methods. Because the outlined methods cannot be practiced on plant cells because of the absence of known plant centromeric sequences, Applicants are not enabled for the generation of plant SATACs.

The DECLARATION 7 of Fabijanski has also been fully considered. DECLARATION 7 discloses repeated methods of DECLARATION 5 along with new photos showing Mendelian inheritance of the SATACs. Fabijanski discloses two generations both of which are constantly exposed to the negative selection agent which would necessarily lead to the maintenance of the fragment for survival of the plant cell. It is not necessary for the fragment to contain a fully functional centromere or indeed a centromere at all for such maintenance, as plasmid and other vectors have often been maintained in the cell under the exposure of a negative selection agent. Evidence is still lacking for the stable maintenance of a fully functioning centromere. Regardless, no such evidence and no such teachings exist in the instant specification. It is repeated that the instant specification does disclose the incorporation of a fully functional centromere in mammalian cells, and does so on page 82 of the instant specification with generations under no selection pressure.

Applicants also urge that Willard does not take into account the teachings of the instant application and thus, does not provide the general state of the art with respect to satellite artificial chromosomes (page 11 of response).

This is not persuasive because the article by Willard is presented in a peer-reviewed journal and is recognized by those of high skill in the art to be a review article

on the state of artificial chromosomes. A mere dismissal by Applicants is not sufficient to dismiss the cited state of the art in peer-reviewed journals. The teaching of Willard of the importance of the centromere is even echoed in the instant application. The general state of the art in artificial chromosome technology is applicable to the instant set of claims especially where the specification is silent with regard to any differences in protocol between animal and plant chromosomes.

Applicants urge that the teachings of Ferl et al do not provide any teachings that suggest the disclosed DNA content differences would have any impact on the ability to produce SATACs from any species, And the species variation in centromere sequences has no bearing on the predictability of the plant SATACs (pages 11-12 of response).

This is not persuasive because the art demonstrates several differences in the DNA content and makeup of plants versus those of animals. The art further supports that there would be no reasonable expectation of success using the instantly claimed methods on plant cells or plant protoplasts. Applicants are required to give full guidance to the claimed species and demonstrate the functionality of their invention. This is not demonstrated anywhere in the specification, and even the disclosures of the DECLARATIONs do not give the detailed evidence provided in the specification for the generation of mammalian SATACs. As stated numerous times before, in order for one of skill in the art to know they have a fully functioning plant centromere they would need particular guidance in identifying said structure. There are no centromeric sequences disclosed in the instant application, or in the declarations that would provide the tools necessary to practice the invention according to the specification.

Applicants urge that the citation of Hall et al is irrelevant because the methods for making satellite artificial chromosomes require no knowledge of the centromeric sequences (page 12 of response).

This is not persuasive because some evidence is required to demonstrate that functioning embodiments are arrived at from the claimed methods. As discussed above, knowledge of the centromeric sequence is required to show stable transmission of SATACs. It was precisely this knowledge of centromeric sequence in for mammalian SATACs that demonstrated that the SATACs had fully functioning centromeres combined with the maintenance of cells containing the SATACs under nonselective conditions.

Applicants urge that the citation of Bryant et al supporting that origins of replication of plants were unknown at the time is irrelevant because knowledge of such a sequence is not required to generate plant SATACs (page 12 of response).

This is not persuasive because the origin of replication is a required element of the SATAC as defined by Applicant on page 17, and without such sequence knowledge one can not definitively demonstrate the presence of the required element. It is noted that Applicants provide exemplary sequences for the origin of replication for mammalian cells. Furthermore, even if it were not required to posses the sequence for the origin of replication, Bryant et al is also cited to present the general state of the art regarding essential chromosomal elements. The fact that plant origins of replication were unknown at the time further evidences the unpredictability of applying the methods used on mammalian cells on plant cells.

Applicants urge that the citation of Avramova et al demonstrating differences in the chromosomal structures of animals and plants is inapt since Avramova et al state that heterochromatin is present in the centromeric and pericentric regions of the chromosomes (pages 12 and 13 of response).

This is not persuasive because Avramova et al demonstrate that there are no similar proteins associated with plants as those demonstrated in animals. The location of the heterochromatin is not the issue, but rather the very distinct differences in plant and animal chromosomes. Avramova et al further demonstrate the high unpredictability that would be present in applying any chromosmal techniques in animals to plants.

Applicants further urge that the instant methods exploit processes common to plants and animals cells and that the DECLARATIONS of record clearly demonstrate this. Applicants also urge that the references do not take into account the technology of the instant specification (page 13 of response).

This is not persuasive because as demonstrated by the cited art, there are numerous differences between plant and animal chromosomes, both sequence and structure-wise. The DECLARATIONS of record incorporate methods not taught in the specification and also do not utilize the same methods of identification that are used for the generation of mammalian SATACs. Furthermore, the references that are cited give a general account of the state of the art regarding artificial chromosomes, most particularly as it involves centromeres and origins of replication, REQUIRED elements as admitted by Applicants of the SATACs that are in the instant claims.

Applicants urge that the methods of the instant application are generally applicable and contain nothing that is peculiar to animal cells (page 13 of response).

This is not persuasive because the application is replete with detailed descriptions of mammalian cell lines, mammalian centromeric sequences and origin of replication sequences. Furthermore the instant specification details, as discussed above, the identification of the required essential SATAC elements with said sequenes, a crucial step in following the functioning embodiments of the invention.

Applicants urge that DECLARATION 7 demonstrates the methods are highly reproducible since a number of different SATACs were generated by several research groups and that Agrisoma, the licensee of the instant application, practices the methods as described in the instant specification and that the basic methods employed are fundamentally the same as in the original application (page 13 of response).

This is not persuasive because it is not enough for the methods to be fundamentally the same as in the original application. For Applicants to be enabled for the generation of plant SATACs one of skill in the art would have to be able to practice the invention based only on the teachings of the instant application with no undue experimentation and no substantial differences in methodology. The instant application does not discuss nor detail the differences required for SATAC identification, nor does it guide one as to how to identify the particular feature of a plant SATAC in the absence of the sequences that are used for the identification of mammalian SATACs as disclosed in the instant application. Furthermore, the instant application gives detailed teachings for differences in mammalian cell lines and changes necessary to practice the invention

(particularly pages 126-128 of the instant application), but does not provide similar guidance for plant cells. As discussed in the prior office actions and as discussed above, the cited art shows the large differences between plant and animal chromosomes and that differences then, between plant and animals cells would likely affect the ratios and concentrations of the method materials as outlined in pages 126-128 of the instant application. However, there is no guidance as to what changes would be necessary. The experimentation could not be routine, because as acknowledged by Applicants, the methods are not common to the prior art and therefore there could be no reasonably expectation of success. Therefore any experimentation to get the instant methods to work on plants would be undue.

Response to Rebuttal to Examiner's comments

Applicants urge that knowledge of the centromere sequence is not required to practice the invention (page 14 of response).

This is not persuasive as detailed above. Applicants maintain that the SATAC has a fully functioning centromere, but without centromeric sequences to visualize the presence of the centromere, one cannot be sure that a fully functioning centromere is present. There are no sequences from plants other than the rDNA that are given in the specification or DECLARATIONS. Even in the absence of centromeric sequences, the instant methods use sequences known to be near the centromeres to establish that the centromere has been incorporated into the SATAC. No such sequences are described or mentioned for plants. Establishing that a fully functioning centromere is present is

essential to providing evidence that a SATAC results from the claimed methods, therefore knowledge of the centromeric sequence is crucial to the invention.

Applicants urge that knowledge of the structure or function of the centromere will not in any way contribute to the success of the method (page 14 of response).

This is not persuasive because the instant specification teaches away from this. As detailed above, applicants take full advantage of the knowledge of centromeric sequences in mammalian cells and even discuss the chromosome-specific centromeric sequences of human chromosomes. While the centromeric sequence may not be required for targeting purposes, it is required to readily determine the presence of the centromere in the SATAC.

Applicants urge that the DECLARATIONS demonstrate the stable inheritance of the SATACS even without the need for selection, proving, beyond any doubt, that the SATAC is as stable as a native chromosome (page 15 of response).

This is not persuasive because DECLARATION 7 does not state anywhere that at any stage, negative selection is absent. In fact, in the materials and methods it quite clearly states that the second generation "seedlings were grown in the presence of L-PPT". Contrary to the mere assertion, the DECLARATION does not provide definitive proof of the stable inheritance of the SATAC in the absence of a negative selection marker. Furthermore, even if such proof were in the DECLARATION, it does not cure the deficiency in the specification for such teaching.

Applicant urges that DECLARATION 2 by Fabijanski states that SATACs in calli were stably maintained in culture for over six months (page 15 of response).

This is not persuasive because the growth conditions included a negative selection medium. As discussed above, the presence of a DNA fragment containing a resistance gene maintained in plants or cells with the application of a negative selection agent does not give evidence of a functioning centromere.

Applicants urge that DECLARATION 3 by Fabijanski discloses the regeneration of 50 hybrid plants expressing the marker genes expressed from the SATAC and the transmission through thousands of cell divisions and regeneration into a whole plant (page 15 of response).

This is not persuasive, the expression of marker genes is not evidence of a SATAC but merely that the plant retains the marker gene because incorporation of the vector into an endogenous plant chromosome would result in the same phenotype even without the presence of a SATAC.

Applicants urge that there is no better test of chromosome stability than its presence in generation after generation (page 16 of response).

This is not persuasive because Applicants has not provided such results in the instant specification. Applicants have only provided such evidence in the form of DECLARATIONS which can not take the place of the specification in establishing enablement. Furthermore, Applicants have not shown stable transmission in subsequent generations beyond the second generation, have not shown such generations in the absence of negative selection pressure, and have not show such stable transmission in a high enough number of plants to suggest the presence of a fully functioning centromere in the SATACs.

Applicants urge that the DECLARATION 5 of Fabijanski uses methods exactly as set forth in the specification, coupled with what was known to one skilled in the art as of the earliest priority date (pages 16-17 or response).

This is not persuasive because the methods set forth in the specification include many steps specific to mammalian cell lines and mammalian cells. There is no "routine in the art" as it applies to generating SATACs in plants as discussed above. The manipulation of plant chromosomes and the identification of plant chromosomal structures was unknown in the art at the time of filing. Therefore, it is not sufficient to merely state that any changes to the methods of the instant specification were what was known to one skilled in the art. The introduction of heterologous DNA into plant protoplasts was known in the art. However, the destablization of chromosomes, the creation of artificial chromosomes, and the isolation of artificial chromosomes was not known in the art. Therefore, even minor changes in any of those parts of the method steps would be required to be in the specification to fully enable one of skill in the art to practice the invention.

Applicants urge that cytological techniques are not crucial for isolating SATACs but are merely useful for visual characterization of SATACs (page 17 of response).

This is not persuasive because without plant specific sequences and without cytological techniques there is literally no way to ascertain that a plant cell would have a SATAC in it, and any method of isolation of a SATAC applied without such visualization or confirmation of a SATAC would not necessarily result in the successful isolation of a

SATAC. It is a requirement for SATAC isolation to first have identification that a SATAC is present. The methods in the instant application even require such verification.

Applicants urge that in situ hybridization performed on plant cells were well known at the time of filing the instant application (page 17 of response).

This is not persuasive because even though in situ hybridization had been performed successfully on some plant species at the time of filing, Applicants are reminded that the scope of their claims include all plant species, all types of plant cells and plant tissues. Furthermore, the visualization of a single gene marker was not routine in the art using fluorescence *in situ* hybridization at the time of filing in plant cells, Particularly where such markers are located near heterochromatic regions.

Applicants urge that DECLARATION 5 discloses methods exemplified in the specification (page 18 of response).

This is not persuasive because the specification goes into much greater detail with it's method steps than DECLARATION 5 does. The specification outlines the use of BrdU as well as a series of steps involved in creating megachromosomes and gigachoromosomes, sorting cells containing each and treating the cells to induce the breakage of dicentric chromosomes. Applicants continue to assert that the exact same methods are used, but also continue to show differences in even basic steps of the method. As stated above, mouse chromosome 7 was identified using G-banding patterns, and mouse centromeric regions were identified using alphoid satellite DNA probes. Neither tool was available for similar identification of particular chromosomes or centromeric regions in plants. So the methodology of identification and tracking the

SATACs is considerably different, and one of skill in the art would not have been guided by the specification to modify as Applicants have done. More than routine experimentation is required and more steps are required to be sure one has a functioning centromere and thus, actually have a functioning embodiment of the invention.

Applicants urge that the questioning of DECLARATION 5 evidencing the generation of SATACs because of unexplained background staining and presence of constrictions is inappropriate and may not be challenged unless those of skill in the art would consider the assertion to have no reasonable scientific basis (page 18 of response).This is not persuasive because the specification does not give guidance for the generation of plant SATACs. The specification does not even mention a plant SATAC and only vaguely mentions that one may use the same methods in the specification on plant cells. The DECLARATIONS submitted are to provide evidence that the same method steps in the specification as used on mammalian cells were employed to generate SATACs in plants. In mammalian cells evidence of SATAC generation included definitive identification of centromeric DNA. DECLARATION 5 while asserting the presence of a centromere, does not provide the same definitive identification. The Examiner stated on the record that the veracity of the statements in the DECLARATION were not being questioned, merely the weight of the evidence and whether or not it supports that there is sufficient guidance in the specification to practice the invention.

Applicants urge that the Examiner has no reason to doubt the factual assertions of Fabijanski (page 18-19 of response).

This is not persuasive because the assertions of Fabijanski are not commensurate with what was used in the specification for the identification of SATACs. The specification details the use of G-banding patterns, centromeric DNA probes, and the absence of negative selection to definitively show the presence of SATACs in mammalian cells. None of these tools are employed in the DECLARATION of Fabijanski. These tools are required to differentiate between functioning and non-functioning embodiments.

Applicants urge that DECLARATION 6 of Hadlaczky was provided to evidence the universality of the chromosomal processes involved in the generation of SATACs and that the method is based on the fundamental process of chromosomal replication common to plants and animals (pages 19-20 of response).

This is not persuasive as it pertains to enablement because the detailed methods outlined by the specification as they apply to mammalian cells including human, mouse and hamster is not in question. It is recognized in the art that there are many similarities in the sequences and proteins involved in these processes in mammalian cells. It is likewise recognized as cited in previous office actions that the sequences and proteins involved in these processes in plants are in fact, different. Therefore, it is merely an opinion stated by Hadlaczky that these same methods should work in plants as well as mammalian systems. Hadlaczky does not take these differences into account, and it is

not sufficient to state the cellular processes are fundamentally the same when the elements required for the invention are known to be different.

Applicants urge that the introduction of SATACs into plant cells is commensurate in scope with the claimed subject matter (pages 20-21 of the response).

This is not persuasive for the reasons outlined above, in particular that the same methods and materials are not available for plants that are available for mammalian cells. Also, as identification of the SATAC is required to practice the invention, methods of identification must be commensurate in scope. In order for one of skill in the art to practice the invention as exemplified in mammalian cells, one would have to isolate and sequence centromeric sequences from plants and use those sequences as probes in identifying the SATAC. Such isolation and sequencing at the time of filing of the invention was not routine in the art, and thus to ascertain that clones actually contain centromeric DNA would have been difficult and required undue trial and error experimentation given that there was no known functional correlation and no known similarity to other centromeric sequences at the time of invention.

Applicants urge that the generation of plant SATACs are not unpredictable because the state of the art is silent regarding SATACs (pages 21-23 of response).

This is not persuasive because the state of the art clearly illustrates the many differences between plants and animals regarding chromosomal sequences and structures including associated proteins. The cited differences would make unpredictable the use of any materials from mammalian cells or chromosomes in the generation of plant SATACs, and undue experimentation to obtain the similar materials

from plants. As to the DECLARATIONS it has been stated on the record before, and continues to be the case that for proper guidance to be given, the information must be contained in the specification, the DECLARATION may not substitute for the specification but must demonstrate the techniques and methods set forth in the specification. Regarding the state of the art, the cited art shows numerous expectations of differences between plant and animal chromosomes and centromere sequences. The specification does not address these expected differences nor provide guidance on how to overcome these differences (particularly in regard to the absence of centromeric sequences in plants for SATAC identification). While the DECLARATIONS give some guidance in this matter, it is a requirement that this guidance be present in the original specification. Furthermore, Applicants have failed to provide evidence that the state of the art as presented by the Examiner is incorrect as it regards the generation of artificial chromosomes and relies purely on the instant application and DECLARATIONS submitted.

Applicants urge that the generation of SATACs is thoroughly described in the specification with numerous examples of particular embodiments (pages 23-24 of response).

This is not persuasive because the detailed descriptions do not apply to plant SATACs in the identification of SATACs, the functioning embodiments of the invention, as discussed in detail above.

Applicants urge the teachings of DECLARATION 7.

This is not persuasive for the reasons discussed above pertaining to enablement. It is believed that DECLARATION 7 has been discussed in detail above and that the urgings on pages 24-25 regarding this declaration have been addressed repeatedly.

Written Description

Claims 50-52, 73-79, 81, 84, 87-95, 97-99, 101, 104, 108, 111, 114-115, 117 and 119-121 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims remain rejected for the reasons of record in the office actions filed 01/17/2003, 10/22/2003, 08/12/2004, 05/09/2005, 03/30/2006, and 07/31/2007 as well as the reasons presented below.

Applicant's arguments filed 01/31/2008 have been fully considered but they are not persuasive.

Applicants urge that the description of SATACs and methods of generating SATACs in the specification are generic and not limited to a single species, and further that exemplary SATACs and cell lines are deposited (page 25 of response).

This is not persuasive because the detailed descriptions of SATACs and generating SATACs as well as the deposited materials applies to mammalian cells and the generation of SATACs in mammalian cells. There is not so much as a single cell-

line or seed deposited from even a single plant species, although the claims are broadly drawn to the generation of SATACs in ANY plant species.

Applicants urge that the specification teaches that the methods are applicable to plants (pages 25-26 of response).

This is not persuasive because a mere assertion does not adequately describe nor show possession of the claimed embodiment. While several generic techniques are listed in the specification, no mention is made of potential modifications that would be required for any plant species.

Applicants urge that plant SATACs have the same structural elements as described for mammalian artificial chromosomes, except that they have a plant centromere (pages 26-27 of response).

This is not persuasive as it pertains to the description requirement, because the admitted different structure is not in any way described in the specification. The specification quite clearly states that the required elements of a SATAC include "at least the centromere and the origins of replication" as stated on page 17 of the specification. However only the sequences required for function in mammalian cells is described. There is no disclosure of any plant sequences for either required structure, and therefore there is no description of 2 of the required structures of the instant invention.

Applicants urge that the structural and functional features of SATACs including plant SATACs are described in the instant application in great detail (page 27 of response).

This is not persuasive because the specification does not describe plant centromeres or plant origins of replications at all, much less "in detail". Applicant has been repeatedly invited to point out where in the specification such description is located. There is no description of sequences and there is no description of what part of the centromere is required for function.

Applicants also urge that the specification describes the structural features that are common to the genus (pages 27-28 of response).

This is not persuasive because the specification does not describe the structural features of the centromeres or the origins of replication that are required for function. Indeed, these structural features were unknown at the time of filing, particularly as it regards the plant sequences and structural features. As Applicants have identified centromeres and origins of replication as required structures for SATAC function, it is incumbent on Applicants to adequately describe the structural features for the claimed embodiments, or at the very least identify the structural features that each species shares that is required for function. While these structural features have been described and disclosed for mammalian centromeres and origins of replication in the form of SEQ IDs, these structures have not been disclosed for plant centromeres or origins of replication, nor have any identifying characteristics of such sequences been identified or described by Applicant.

Applicants urge that the DECLARATIONS demonstrate that "all of one of skill in the art has to do is introduce a DNA fragment into a cell, grow the cell under selective

conditions and 'poof' SATACs and/or precursors or intermediates thereof are produced by the cell (page 28 of response).

This is not persuasive because the specification and DECLARATIONS do not teach introducing just any fragment of DNA into a cell, and in fact have strict requirements on targeting sequences as well as the requirement of selectable marker to be included in the introduced fragment. Furthermore, in order to identify SATACs, precursors, or intermediates, one must know the structural features of each, and how to identify those features to be certain the cell contains them before moving on to the next step of maintaining them and thus, critical elements required for identification to ensure that one has indeed produced a SATAC, are not described in the specification for plants.

Applicants urge that the citation of Amgen Inc v. Chugai Pharmaceuticals regarding written description is inapt because even one of the patents held to be valid that claimed a purified and isolated DNA sequence consisting essentially of a DNA sequence encoding erythropoietin (page 28 of response).

This is not persuasive because the ruling held that the chemical and physical properties of the product must be known. The case and claim cited by Applicant refers to a known protein sequence that would have a finite, limited, number of DNA embodiments that would be known to encode a known protein sequence. In the instant case, Applicants have not correlated any structural feature with any sequence, and further have not established a finite, limited number of possibilities regarding this required feature of their invention, as it regards plant centromeric sequences. As

established above and in prior office actions, plant centromeric sequences were unknown at the time of invention, and structural features and correlating sequences were also unknown. Only a comparison at the most basic level between that of animal and plant centromere function has been made, and such a basic comparison does not in any way describe the necessary features of the required element in such a way as to establish that Applicants were in possession of such a feature.

Applicants urge that the actual physical embodiments of a plant SATAC are identified in the instant application and that the DECLARATIONS herein discussed above and in previous office actions demonstrate such embodiments (page 28 of response).

This is not persuasive because these embodiments are not contained within the original specification and are not thus identified in the original specification. Additionally, the "entire plant artificial chromosome hybrid" is not revealed by the DECLARATIONS as urged by Applicant because two of the required features of such an embodiment, the centromere and the origins of replication, are not definitively identified.

Applicants urge that pertinence of the citation of MPEP 2163 is not clear as the instant specification provides detailed description of the structure of SATACs, and how to prepare, identify and isolate them (page 29 of response).

This is not persuasive because the written description requirement over such a broad genus cannot be satisfied with the deposit of cells from a single species especially where the state of the art clearly establishes major differences between

groupings of species. There was no art recognized correlation of structure with centromeric function at the time of filing, and therefore the citation and rejection stand as applied to all the claims above.

Applicants urge that the written decription requirement can be satisfied without providing representative species of every type of satellite artificial chromosome if the descriptions provided are descriptive of all satellite artificial chromosomes (page 29 of repsonse).

This is not persuasive because Applicants demonstrated possession of mammalian SATACs by using mammalian centromeric sequences as probes to show the existence of centromeres in the generated mammalian SATACs. As discussed above the sequences shown for mammalian centromeres are not representative of plant centromeres, and thus, the description requirement is not satisfied for the generation of plant SATACs.

Response to Rebuttal to Examiner's comments

Applicants urge that the specification describes a universal process for the generation of SATACs (pages 30-32).

This is not persuasive because the detail in describing the mammalian exemplary example, employs the use of centromeric sequences to identify SATACs and to show that the SATACs were functional SATACs in that they contained a mammalian centromere. There is no description of similar sequences in plants, and there is no

description of how to show that the SATAC contains a centromere (a required element of the SATAC according to the specification) for species where such sequences are not known. Furthermore it becomes unclear which methods are required to practice the invention with plants, as with mammalian cells, an application of BrdU was employed for destabilization. No mention of this step or any such similar step is made in any of the DECLARATIONS of record and it is not clear from the specification whether or not this step is required.

Applicants urge that the DECLARATIONS provide evidence of generation of SATACs in plants as described in the application (pages 32-33 of response).

This is not persuasive because numerous differences between the methods of the specification and the DECLARATIONS of record have been noted. As described in detail above the largest difference is in the identification of the centromere of the SATAC, a step that is required to prove possession, and a functional element that is required in order for a DNA fragment to be termed a SATAC according to Applicant. In addition to the absence of a positive identifier of the plant centromere, the DECLARATIONS of record also fail to show stable maintenance of SATACs in the absence of negative selection pressure. This is a feature appreciated by Applicants as evidence of the stable maintenance of mammalian centromeres was shown in the instant application with subsequent generations in the absence of a negative selection marker.

Applicants urge that no knowledge of the centromere sequence is required.

This is not persuasive for the reasons of record and for the reasons stated above. It is believed that this argument has been fully discussed in the prior paragraphs of this office action.

Claim Rejections - 35 USC § 102

The rejection of claims 50-52, 73, 80, 88-92, 94-96, 98-100, 107, 114, 117-118 and 120-122 under 35 USC 102 (b) as being anticipated by Richards et al is hereby withdrawn in response to Applicants' arguments when taken together with the claim amendments.

Double Patenting

Claims 92, 95, 99 and 114-155 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 52 and 66 of copending Application No. 10287313.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants urge that claims 12,13,19,26,53 and 54 of copending application 10287313 are drawn to products.

This is found to be persuasive and these claims have been taken out of the provisional rejection.

Applicants urge that claims 52 and 66 are likely to be cancelled.

This is not persuasive since these claims have not yet been cancelled.

Claims 92, 95, 99 and 114-155 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 63 of copending Application No. 11284877.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants urge that claims 53, 65, 69-70, 73 and 76 from copending application 11284877 have been cancelled.

This is found persuasive and these claims have been removed from the provisional rejection.

Applicants urge that claim 63 is likely to be cancelled.

This is not persuasive because the claim has not been cancelled.

No claims are allowed.

The claims are free of the prior art given the failure of the prior art to teach or reasonably suggest a satellite artificial chromosome with substantially more heterochromatin than euchromatin.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRENT PAGE whose telephone number is (571)272-5914. The examiner can normally be reached on Monday-Friday 8-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on (571)-272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brent T Page
/Russell Kallis/
Primary Examiner, Art Unit 1638